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REVIEW

Can Statins Reduce Perioperative Morbidity and Mortality in Patients Undergoing Non-Cardiac Vascular Surgery?

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Aims. *To determine whether statins can reduce perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery.*
Methods. *A search using Pubmed was performed to identify reports in English. The search terms were: "statins", "perioperative morbidity", "perioperative mortality" and "vascular surgery". We excluded studies dealing with the effect of statins in cardiac surgery. Retrieved articles were manually searched.*
Results. *Current evidence shows that statins decrease perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery. Any benefit probably occurs soon (within a month) after initiating treatment.*
Conclusions. *Appropriately designed trials need to confirm the beneficial effect of perioperative statin therapy in various patient categories. The optimal duration and dose of perioperative statin therapy should be defined.*

Keywords: Statins; Cardiovascular disease; Perioperative mortality; Vascular surgery.

Introduction

The prevalence of vascular complications is as high as 5.6% in non-cardiac operations.[1] Therefore, as many as 1 million surgical procedures may be complicated by perioperative vascular events every year.[2] Complications, such as atrial fibrillation,[3–4] ventricular arrhythmias,[5] pulmonary edema[6] and myocardial infarction (MI),[6–8] are the main causes of increased perioperative,[7,8] as well as long-term,[9] morbidity and mortality in patients undergoing major elective non-cardiac surgery. Postoperative myocardial ischaemic events are common in high-risk patients (e.g. those with coronary heart disease) undergoing non-cardiac surgery.[10] Lee *et al.* analyzed the risk of major cardiac complications (MI, cardiogenic pulmonary edema, cardiac arrest and cardiac death) in 4315 patients undergoing non-cardiac surgery.[11] The Lee index can predict major cardiac complications and cardiovascular death in patients undergoing non-cardiac surgery,[12] but its classification of procedures seems suboptimal.

MI is a cause of perioperative morbidity and mortality after vascular surgery[2,13] that may remain unrecognised.[11,14–16] Although the incidence of perioperative MI among patients undergoing major non-cardiac surgery is 2–3%, rates among those undergoing major vascular surgery can reach 34%.[7,16] Endovascular surgery may be associated with reduced perioperative complications compared with open surgery, although this does not apply to late cardiac events.[17] Perioperative MI is also associated with prolonged hospital stay and morbidity and mortality rates as high as 25–40%.[18,19]

Various drugs may reduce vascular events in patients undergoing major elective vascular surgery. These include beta-blockers,[7,8,20–25] calcium-channel blockers,[26] α_2-adrenergic agonists,[27–29] and aspirin.[30] However, no globally accepted guidelines have been formulated.[31] It follows that patients undergoing elective vascular surgery are often underprotected.[32]

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Statins can stabilize coronary plaques,[33–36] and exert anti-inflammatory antithrombogenic, antiproliferative and leucocyte-adhesion inhibiting effects.[37–44] Therefore, statins can prevent vascular complications,[45] possibly cost-effectively.[46]

Methods

We searched PubMed for studies in English using the terms ''statins'', ''perioperative morbidity'', ''perioperative mortality'' and ''vascular surgery''. We excluded articles dealing with cardiac surgery or percutaneous intervention. The relevant articles were manually searched for additional studies.

Results

Perioperative statin therapy and morbidity/mortality rates

Trials that investigated the effect of perioperative statin therapy on morbidity and mortality in patients undergoing non-cardiac vascular surgery are shown in Table 1.

In a retrospective case-control study including 2816 patients undergoing major non-cardiac vascular surgery (acute or elective abdominal aortic aneurysm repair, carotid endarterectomy [CEA], lower extremity revascularization),[47] perioperative statin use was associated with a > 4-fold reduced risk in perioperative mortality [adjusted odds ratio (OR) = 0.22, 95% confidence interval (CI) = 0.10–0.47]. This finding was supported by a prospective, randomized, placebo-controlled, double-blind trial assessing the effect of atorvastatin (20 mg/day) for 45 days on perioperative cardiovascular events after vascular surgery compared with placebo.[48] Vascular surgery was performed not earlier than 2 weeks after randomization (average 31 days after starting medication). All patients were followed for 6 months after surgery. Despite the small number of patients (50/group), a more than three-fold risk reduction was observed for statin users vs. placebo (8.0% vs. 26.0%, $p = 0.031$). The rate of combined end points (death from cardiac causes, nonfatal acute MI, ischemic stroke and unstable angina) was 9.1% in the atorvastatin group and 28.3% in the placebo group ($p = 0.030$).

The beneficial effect of statins and non-statin lipid-lowering agents was reported in a large, retrospective cohort study including 780 591 patients undergoing major non-cardiac surgery.[49] Of these, 65 399 patients underwent vascular surgery; 13 862 patients were statin users. Statin use was associated with a significant ($p < 0.001$) reduction in perioperative mortality in patients undergoing not only vascular, but also any non-cardiac surgery.

A study [Statins for Risk Reduction in Surgery (StaRRS)] assessing the effect of statins on cardiac complications (death, MI, myocardial ischemia, ventricular tachyarrhythmias and acute congestive heart failure) in patients undergoing non-cardiac vascular surgery (CEA, aortic surgery, or lower extremity revascularization) supported the use of perioperative statin therapy.[50] Complications occurred in 157 of 1163 eligible hospitalizations. A multivariate model (accounting for age, gender, body mass index, type of operation, whether surgery was urgent or elective, diabetes mellitus and left ventricular dysfunction) showed that statins were beneficial (OR = 0.52, 95% CI = 0.35–0.76, $p = 0.001$).

Another trial included 1566 patients undergoing CEA (1440 patients) or CEA combined with coronary artery bypass grafting (CABG, 126 patients). Perioperative statin (20 ± 10 mg/day atorvastatin [332 patients], 20 ± 10 mg/day simvastatin [189 patients], 30 ± 20 mg/day pravastatin [91 patients], 30 ± 10 mg/day lovastatin [32 patients] or 30 ± 10 mg/day fluvastatin [13 patients]) use in 657 (42%) patients significantly reduced the incidence of cerebrovascular events and mortality.[51] In multivariate analysis, adjusting for comorbidities associated with stroke (symptomatic carotid artery disease, chronic atrial fibrillation, hyperlipidemia, intraluminal shunt and patch graft use and combined CEA/CAGB), statin use was associated with reduced odds of perioperative stroke (OR = 0.29, 95% CI = 0.14–0.61, $p < 0.05$).[51] Similarly, in multivariate analysis of perioperative mortality, adjusting for comorbidities (percentage carotid stenosis, hypertension, chronic atrial fibrillation, coronary artery disease, congestive heart failure, chronic renal insufficiency, use of β-blockers, and combined CEA/CABG), statins reduced perioperative death (OR = 0.14, 95% CI = 0.03–0.62, $p < 0.05$).[51] An observational study verified the protective effect of statins in patients undergoing CEA (Table 1).[52] However, as the authors underlined, these results need to be confirmed in randomized controlled trials.

The long-term benefit of statins was reported in patients undergoing successful abdominal aortic aneurysm (AAA) surgery.[53–55] A 6.3% risk for cardiac death and MI at 2 years,[54] and a 28% incidence for death due to cardiovascular causes at 8 years[55] following aortic operations have been reported. After a median follow-up of 4.7 years, patients using statins (154 of 510 followed-up patients) had a 2.5-fold reduction

Table 1. Trials assessing the effect of statin therapy on perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery

Study (Year)	Number of patients	Study Design	Statin used	Type of operation	Outcome
Poldermans *et al.*[47] (2004)	**2816**	Retrospective case-controlled study including 2816 patients, 160 case subjects were identified who died because of any cause during surgery or during post-operative hospital stay <30 days. For each case subject, 2 controls were selected (one before and one after the case), i.e. 320 patients formed the control group.	NM	− Acute AAA repair: **38%** − Elective AAA repair: **48%** − CEA: **4%** − Lower extremity revascularization: **11%**	Perioperative mortality was reduced 4.5 times compared to non-users (adjusted OR = 0.22, 95% CI = 0.10−0.47)
Durazzo *et al.*[48] (2004)	**100** 50 statin-users and 50 placebo	Prospective, randomised, placebo-controlled, double blind trial.	Atorvastatin 20 mg/day or placebo for 45 days.	− AAA repair: **28% vs. 26%*** − Infrainguinal arterial bypass: **18% vs. 22%*** − CEA: **12% vs. 10%*** − Amputation: **2% vs. 4%*** − No operation: **12% vs. 8%*** * Percentages are given for patients on atorvastatin vs. placebo	Overall rate of combined endpoints of death from cardiac causes, nonfatal acute MI, ischemic stroke and unstable angina was 8.0% vs. 26.0%, in the atorvastatin and placebo groups, respectively ($p = 0.031$).
Lindenauer *et al.*[49] (2004)	For vascular surgery procedures: **65399** 13862 statin users vs. 51537 non-users	Retrospective cohort study including 780591 patients undergoing major non-cardiac surgery (vascular, orthopedic, abdominal, thoracic, gynecologic, urologic, neurosurgical, otolaryngologic, transplant, trauma, and plastic and reconstructive)	NM	NM	For the whole study statin use was associated with a significant ($p < 0.001$) reduction in perioperative mortality (1595 users vs. 4158 non-users, $p < 0.001$). Results were not provided for each type of operation.
O'Neil-Callahan *et al.*[50] (2005)	**1163**	Retrospective study of CEAs, aortic surgery (aorto-iliac bypass, AAA or dissection repair), or peripheral lower extremity revascularization procedures. A total of 1163 hospitalizations on 997 patients were included in the study.	NM	− CEA: **31.3%** − Aortic Surgery (aorto-iliac bypass, AAA, dissection repair): **15.2%** − Lower extremity revascularization: **53.5%**	Statin use associated with a significant reduction in the rate of complications in both univariate (OR = 0.56, 95% CI = 0.39−0.79, $p = 0.001$) and multi-variate (OR = 0.52, 95% CI = 0.35−0.76, $p = 0.001$) analyses.
McGirt *et al.*[51] (2005)	**1566** 657 statin users vs. 909 non-users (42% vs. 58%)	Retrospective study	Atorvastatin: **332 pts** Simvastatin: **189 pts** Pravastatin: **91 pts** Lovastatin: **32 pts** Fluvastatin: **13 pts**	CEA	Statin use associated with a reduction in perioperative strokes (1.2% vs. 4.5%, $p < 0.01$), peri-operative TIAs (1.5% vs. 3.6%, $p < 0.01$), mortality (0.3% vs. 2.1%, $p < 0.01$), and the median (inter-quartile range) length of hospitalisation (2 days [2−5 days] vs. 3 days [2−7 days], $p < 0.05$)

Kennedy *et al.*[52] (2005)	**3283 CEAs** 1252 Asymptomatic (665 statin users), 2031 Symptomatic (815 statin users)	Observational Study	NM	CEA	When patients were matched to reduce the bias in estimation of potential treatment effect, statin use was associated with absolute reductions in in-hospital mortality rate of 0.9% ($p = 0.005$), 0.8% ($p = 0.0034$), and 0.9% ($p = 0.016$) using the kernal, stratified and radius matching methods, respectively. The reductions associated with statin use for in-hospital ischemic stroke or death rates were 1.7% ($p = 0.022$), 1.5% ($p = 0.055$) and 1.7% ($p = 0.038$), respectively
Kertai *et al.*[53] (2004)	**510** 154 statin users (30%)	Retrospective study. Although 570 patients initially underwent AAA repair, 519 (91%) survived surgery for at least 30 days and a total of 510 patients were followed-up until the end of the study period [Median follow-up period: **4.7 years** (interquartile range, **2.7 to 7.3 years**)]	Simvastatin: **110 pts, 71%** Atorvastatin: **27 pts, 18%** Pravastatin: **16 pts, 10%** Fluvastatin: **1 pt, 1%**	AAA repair	After a median follow-up of 4.7 years (interquartile range, 2.7 to 7.3 years), statin use was shown to be associated with a 2.5-fold reduction in the risk of all-cause mortality (HR = 0.4; 95% CI: 0.3–0.5) and more than a threefold reduction in the risk of cardiovascular mortality (HR = 0.3; 95% CI: 0.2 to 0.6)
Parker Ward *et al.*[57] (2005)	**446** 72 statin users vs. 374 non-users	Retrospective analysis of infrainguinal vascular bypass surgeries focusing on the association between preoperative statin and beta-blocker use, perioperative complications and length of hospital stay.	NM	Infrainguinal arterial bypass surgery	Statin use associated with fewer combined cardiovascular complications (6.9% vs. 20.1%, $p < 0.0008$) and a shorter length of stay (6.4 vs. 9.7 days, $p < 0.007$).
Abbruzzese *et al.*[58] (2004)	**172** 88 statin users vs. 84 non-users	A total of 172 patients and 189 grafts were included in the study. Of these, 88 patients (94 grafts) were in the statin group and 84 patients (95 grafts) belonged to the control group.	– Results were provided for limbs, not patients: Simvastatin: **60 limbs, 64%** Atorvastatin: **28 limbs, 30%** Cerivastatin: **1 limb, 1%** Lovastatin: **3 limbs, 3%** Pravastatin: **2 limbs, 2%**	Infrainguinal arterial bypass surgery using autogenous saphenous vein graft	– Perioperative morbidity and mortality did not differ between the 2 groups. – Two-year primary-revised (94% ± 2% vs. 83% ± 5%, $p < 0.02$) and secondary (97% ± 2% vs. 87% ± 4%, $p < 0.02$) graft patency rates were higher for the statin group compared with the control group.
Kertai *et al.*[59] (2004)	**570** 162 statin users	Retrospective study	Simvastatin **71.6%** Atorvastatin **14.8%** Pravastatin **8.6%** Fluvastatin **1.2%** Cerivastatin **3.7%**	AAA repair	Statin users had a 3-fold reduced risk of a composite end-point of 30-day perioperative mortality and nonfatal MI compared with non-users [6 (3.7%) vs. 45 (11.0%) pts, respectively, OR = 0.31, 95% CI = 0.13–0.74, $p = 0.01$)

NM = Not Mentioned, AAA = Abdominal Aortic Aneurysm, CEA = Carotid Endarterectomy, OR = Odds Ratio, CI = Confidence Interval, pts = patients, HR = Hazard Ratio, MI = myocardial infarction.

in all-cause mortality (hazard ratio [HR] = 0.4; 95% CI = 0.3−0.5) and more than a threefold reduction in the risk of vascular mortality (HR = 0.3; 95% CI: 0.2−0.6) compared with non-users (356 of 510 followed-up patients).[53] In the same study, use of β-blockers was also associated with an approximately 1.5-fold reduction in all-cause and vascular mortality compared with non-use thus verifying the results of another study,[51] although an opposite opinion was also expressed.[56] The authors concluded that statin use in patients undergoing successful AAA surgery is associated with a significant reduction in all-cause and vascular mortality. Similar results regarding long-term survival were obtained from preoperative statin therapy in patients undergoing infrainguinal vascular bypass surgery[57] in addition to improved graft patency.[58]

A beneficial effect from using both β-blockers and statins on perioperative (30-day) mortality and non-fatal MI in patients undergoing AAA surgery was demonstrated.[59] In multivariate analysis, patients receiving both medications showed a 4-fold and 3-fold reduction in perioperative mortality and nonfatal MI following AAA surgery, respectively, compared with patients receiving either statins (7.7% vs. 33%, OR = 0.24, 95%CI = 0.10−0.70, $p = 0.01$) or β-blockers (7.7% vs. 20%, OR = 0.24, 95%CI = 0.11−0.54, $p = 0.01$) alone. These results[59] suggest a benefit of combining statins and β-blockers in high-risk patients as defined by a revised cardiac index. The opinion that combined treatment for vascular risk factors results in increased benefit has been reported.[60−61]

A prospective, randomized trial (the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo − IV [DECREASE-IV] Study) is under way.[62] It will determine the impact of perioperative administration of a β-blocker (bisoprolol), a statin (fluvastatin), or both, on 30-day vascular events (including non-fatal MI or any death with a cardiovascular cause: cardiac arrest, MI, pulmonary embolus, stroke, hemorrhage, or death due to unknown causes) following major non-cardiac surgery.

Statins and peripheral arterial disease (PAD)

In patients with PAD, statins improve lower extremity blood flow and lower extremity function (as defined by ankle brachial index),[63−64] as well as subjective symptoms of claudication (e.g. walking time).[65−68] In addition, a retrospective review[57] of infrainguinal vascular bypass surgery in 446 patients showed that preoperative statin use was associated with fewer cardiovascular complications (6.9% vs. 20.1%; $p < 0.008$) and a shorter in-hospital stay compared with non-users (6.4 vs. 9.7; $p = 0.007$). Statin use was a predictor of fewer preoperative combined vascular complications in multivariate analysis (OR = 0.36, 95% CI = 0.14−0.93, $p = 0.035$).

The results that derive from statin use[57] are better compared with the results that derive from perioperative β-blockade use in patients undergoing infrarenal vascular surgery.[24] In this double-blind, randomized, placebo-controlled trial the effect of perioperative β-blockade with metoprolol vs. placebo on patients undergoing infrarenal vascular surgery was investigated.[24] Metoprolol use did not reduce 30-day cardiovascular events (MIs, unstable angina, ventricular tachycardia, stroke) compared with placebo [Adjusted (for sex, age, baseline use of statins and planned aortic cross-clamping) RR = 0.87 (0.48−1.55)]. However, metoprolol significantly reduced the median (95% CI) time between surgery and discharge compared with placebo (9 [8−12] vs. 12 [9−19]) days (adjusted [for sex, age, baseline use of statins and planned use of aortic cross-clamping] HR = 1.71, 95% CI = 1.09−2.66, $p = 0.02$).

It has been suggested that statins exert a renoprotective effect in PAD and other patients.[69−73] There is also evidence that serum creatinine and calculated creatinine clearance are indicators of postoperative mortality.[74] Therefore, the effect of statins on renal function following vascular surgery deserves investigation.

National guidelines regarding the use of statins in PAD were proposed.[75] Similar international guidelines could result in a widely accepted strategy.

Safety of Statin Use

Perioperative statin administration in high-risk patients undergoing major elective vascular surgery seems to be safe[76] and not associated with statin-related myopathy.[77−81] A total of 885 patients (211 statin users) undergoing major elective vascular surgery (527 AAA repair operations and 358 lower extremity revascularization procedures) were studied. Although maximum serum creatine kinase activities were significantly higher in statin users compared with non-users (301 for statin users, range 16−13 377 U/L vs. 192 for non-users, range 8−30 390, $p = 0.003$) the difference became non-significant ($p = 0.142$) when corrected for length of surgery, cardiac risk factors and risk for myopathy. No muscular complaints or case of rhabdomyolysis was observed in either group. In addition, significantly fewer nonfatal MIs (15 vs. 81 and 6.7% vs. 10.8%; $p < 0.01$) and perioperative deaths

(5 vs. 35 and 2.1% vs. 3.9%; $p < 0.01$) occurred in statin users compared with non-users. The combined endpoint of perioperative death and MI occurred in significantly fewer statin users compared with non-users (8.8% vs. 14.4%; $p < 0.01$).

The Future

More evidence is required to confirm the benefit observed in the studies described above. However, the obvious ethical restrictions may mean that we will never see placebo-controlled trials. One option is to evaluate different targets and various lipid-lowering drugs in the perioperative period to establish the optimal choice. For example, the cholesterol lowering effect of statins can be extended by adding ezetimibe, a selective cholesterol transport inhibitor.[82]

The low density lipoprotein cholesterol (LDL-C) target for patients with PAD needs to be established. For this high risk population it would be desirable to achieve the LDL-C target defined by the European and USA guidelines for this category (i.e. 2.5 and 2.6 mmol/l, respectively with an optional target of 1.8 mmol/l for very high risk patients).[83–84]

Conclusions

There is growing evidence suggesting that statin use significantly reduces perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery, in a similar manner to that reported in cardiac surgery,[85–86] as well as in renal,[87–88] heart,[89–90] and lung[91] transplantation operations. However, optimal perioperative statin therapy has not been defined. Appropriately designed trials are needed to define optimal perioperative statin therapy in various categories of patients.

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